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Letter to the Editor

Excited delirium syndrome (ExDS): Redefining an old diagnosis

Dear Editor,

I read with interest the article of Vilke et al. summarizing "the current state and knowledge of the excited delirium syndrome" (ExDS).[1] As mentioned at the end of their paper, ExDS is a "complex issue". According to the American College of Emergency Physicians White Paper on ExDS (ACEPWP), cocaine-induced fatal ExDS, "in chronic cocaine abusers", is "possibly caused by excessive dopamine stimulation in the striatum".[2] However, many mechanisms may be involved in the mortality associated with ExDS. Therefore, I wonder if more emphasis should not be put on the cardiovascular consequences of certain restraint techniques and on intracellular dysfunction induced by drugs and physical exertion.

Under the heading "Acute treatment", the authors comment that "there are no clinical or laboratory data that support that the use of prone or supine restraint will have any negative physiologic impact on these individuals". Roeggla et al. have shown a significant decrease in the cardiac output (37%) when non-obese volunteers at rest, with their ankles and wrists tied behind their back, were changed from the upright to the prone position.[3] Since the submission of the authors' paper, Ho et al. have showed a direct correlation between the decrease of the inferior vena cava diameter and the amount of weight lowered onto the upper back of non-obese volunteers at rest.[4] In this study, the absence of significant change in the heart rate, the systolic and the diastolic blood pressure should not be interpreted as if compression of the upper torso is without any cardiovascular physiological consequences. In fact, no significant changes can occur in the heart rate or the mean arterial pressure while the cardiac index can decrease significantly when healthy volunteers are changed from the supine to the prone position.[5]

Earlier in the article, the authors refer to Dr. Luther Bell. In the medical condition described in 1849 and called "Bell Mania", the hyperactive stage before the fatal demise was lasting "an average of about 8 days".[6] In the last 2 decades, unexpected cardiorespiratory arrests have been reported very rapidly after pressure was applied to the upper torso of individuals restrained in the prone position.[7,8] The ACEPW mentions that "the majority of lethal ExDS die shortly after a violent struggle", "suddenly, typically following physical control measures".[2]

The authors comment that "there is likely to be a subset of patients where early treatment might be life saving" and that first responders are one of the key elements to prevent fatal ExDS. However, the reduction in mortality depends in the understanding of the cardiovascular consequences of their interventions as well as in the recognition of this challenging medical condition.

In ExDS, restraint-related deaths are preceded by a variable period of agitation and physical exertion (dynamic exercise) followed by a period of struggling against restraints (isometric or static exercise). First responders, in a stressful situation, may not realize the magnitude of the pressure applied on the upper torso.[9] By decreasing the venous return by more than 50%, pressure applied to the upper torso may result in a vasovagal syncope.[10] On the other hand, considering that a Valsalva maneuver during a static exercise such as weight lifting can result in syncope,[11] syncope could also occur when a confused individual is forcefully struggling against tight restraints. A protocol issued for first responders mentions that patients in ExDS may be in "constant or near constant physical activity" and "heavy exertion".[1] In a clinical situation where the homeostasis depends on the increased cardiac output, the increased oxygen delivery and the increased minute ventilation, a sudden period of hypotension and/or bradycardia could be poorly tolerated.

The minute ventilation may be as high as 150 L/min in a strenuous exercise. Considering that the decrease in maximal voluntary ventilation in the prone maximal restraint position is less than 20%,[12] the increased minute ventilation, in an individual restrained in the prone position on a hard surface, could also be regarded as an intermittent space-occupying lesion predisposing to an acute abdominal compartment syndrome.[13] Moreover, the diastolic blood pressure may increase dramatically (up to 140 mmHg)[14] during a static exercise lasting more than a few minutes. Such a stressful hemodynamic condition could be poorly tolerated in anyone having a preexisting cardiac pathology such as cardiac enlargement or coronary artery disease.

The authors and the ACEPWP explain the interest in the subset of patients in ExDS, usually associated with stimulant abuse like cocaine, who die hours later from a multiple organ failure syndrome characterized by severe hyperthermia and rhabdomyolysis.[1,2] They mention that the current hypothesis, "central dopamine stimulation", is supported by "the fact that hypothalamic dopamine receptors are responsible for thermoregulation" and that this hypothesis also "provides a link to psychiatric etiologies and the delirious presentation in patients with ExDS".[1] However, many mechanisms (peripheral and central) are involved in the hyperthermic properties of cocaine[15] and increased heat production, in a clinical situation of "constant or near constant physical activity" and "heavy exertion",[1] is not being considered in this hypothesis. Bachmann et al. mentioned recently that "research on the biological underpinnings of mood disorders has therefore moved away from focusing on absolute changes in neurochemicals such as monoamines and neuropeptides".[16] There are accumulating evidences showing that mitochondrial dysfunction

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may have an important role in the pathophysiology of psychiatric illnesses such as bipolar disorders and schizophrenia.[17] Considering that Ruttenber et al. concluded that cocaine-associated rhabdomyolysis and excited delirium were different stages of the same syndrome[18] and that in rhabdomyolysis, "the final common pathway for injury is an increase in intracellular free ionized cytoplasmic and mitochondrial calcium",[19] mitochondrial dysfunction may also play a role in the pathophysiology of ExDS.

Future research should consider the 2 different clinical presentations of fatal ExDS. To help first responders, research should be oriented in the development of rapid, safe and efficient control/restraint techniques respecting the cardiovascular physiological adaptations of dynamic exercise.[14] Research should explore the relationship between sudden deaths of individuals restrained for ExDS and the abdominal compartment syndrome as the prone position and obesity are 2 predisposing factors of both conditions.[13,20] In anesthesiology, "obstruction of the inferior vena cava is a well-recognized complication of prone positioning and is exacerbated by any degree of abdominal compression, leading to a decreased cardiac output".[21] The finding, in Stratton et al. study,[20] that only a minority of individuals died while restrained in the prone position remains an argument for the use of the prone position in ExDS. However, the length of the struggle and whether or not pressure was applied on the upper torso were unknown variables in that study. As pressure on the spine in the prone position can "markedly" obstruct the right ventricular outflow tract in certain circumstances,[22] the surface area and the exact location over which the weight force is applied should be considered important variables in future studies as the pressure generated by a force is inversely proportional to the surface area over which it is applied and the vulnerable structures (inferior vena cava, superior vena cava and heart chambers) have precise locations. Computer simulation could be used to help first responders understand the potential physiological consequences of their interventions as it is unethical or impossible to replicate exactly all the variables involved in real field situations.[8] Considering Lee et al. results[23] and the observation that electrical control devices "are likely to be less efficient on ExDS subjects",[2] technology should be reappraised so that individuals in ExDS may eventually receive, if necessary, a chemical restraint from a certain distance, not painful repetitive electric discharges.

At the cellular level, the mechanism of action of cocaine implies an increase in intracellular calcium in the muscle.[24,25] As there are similarities between certain cases of cocaine-induced ExDS and exertional heat illness and exertional rhabdomyolysis which are characterized by an uncontrolled increase in intracellular calcium,[26] research could explore if certain complications associated with cocaine-induced ExDS could not be the result, in susceptible individuals, of a hypermetabolic syndrome similar to malignant hyperthermia, leading to an imbalance between systemic oxygen delivery and demand resulting in tissue hypoxia. Considering that valproic acid may eventually offer protection against methamphetamine-mediated mitochondrial toxicity in the central nervous system[16] as well as against hypoxic-mediated mitochondrial insult in peripheral organs,[27] future research in ExDS should not focus exclusively on brain neurochemicals.

There is ample evidence to suggest that the mortality associated with ExDS is multifactorial. Excessive dopamine stimulation in the striatum may be an important factor in certain individuals, particularly in chronic cocaine abusers. However, the acute effects of physical restraints and of physical exertion on the cardiovascular physiology and of mitochondrial dysfunction at the cellular level should not be ignored. Although a better understanding of the mechanisms of fatal ExDS will eventually lead to a reduction in mortality, these patients will remain a major challenge for first responders.

Conflict of interest

None declared.

References

1. Vilke GM, Payne-James J, Karch SB. Excited delirium syndrome (ExDS): redefining an old diagnosis. *J Forensic Leg Med* 2012;**19**:7–11.
2. ACEP Excited Delirium Task Force. American College of Emergency Physicians white paper report on excited delirium syndrome. Report to the Council and Board of Directors on excited delirium at the Direction of Amended Resolution 21(08). September 10, 2009. Available at: http://ccpicd.com/Documents/Excited%20Delirium%20Task%20Force.pdf. [accessed 10.02.12].
3. Roeggla M, Wagner A, Muellner M, Bur A, Roeggla H, Hirschl MM, et al. Cardiorespiratory consequences to hobble restraint. *Wien Klin Wochenschr* 1997;**109**:359–61.
4. Ho JD, Dawes DM, Moore JC, Caroon LV, Miner JR. Effect of position and weight force on inferior vena cava diameter-implications for arrest-related death. *Forensic Sci Int* 2011;**212**:256–9.
5. Wadsworth R, Anderton M, Vohra A. The effect of four different surgical prone positions on cardiovascular parameters in healthy volunteers. *Anaesthesia* 1996;**51**:819–22.
6. Mann SC, Caroff SN, Bleier HR, Welz WKR, Kling MA, Hayashida M. Lethal Catatonia. *Am J Psychiatry* 1986;**143**:1374–81.
7. O'Halloran RL, Frank JG. Asphyxial death during prone restraint revisited: a report of 21 cases. *Am J Forensic Med Pathol* 2000;**21**(1):39–52.
8. *Witness says RCMP put knee in Dziekanski's back*. The Canadian Press. Available at: http://www.ctv.ca/CTVNews/CanadaAM/20090210/BC_braidwood_tuesday_090210/; 2009 Feb 10 [accessed 30.09.11].
9. O'Halloran R. Reenactment of circumstances in deaths related to restraint. *Am J Forensic Med Pathol* 2004;**25**:190–3.
10. Hainsworth R. Pathophysiology of syncope. *Clin Auton Res* 2004;**14**(Suppl. 1):18–24.
11. Compton D, Hill PM, Sinclair JD. Weight-lifters' blackout. *Lancet* 1973;**2**(7840):1234–7.
12. Michalewicz BA, Chan TC, Vilke GM, Levy SS, Neuman TS, Kolkhorst FW. Ventilatory and metabolic demands during aggressive physical restraint in healthy adults. *J Forensic Sci* 2007;**52**(1):171–5.
13. Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions. *Intensive Care Med* 2006;**32**:1722–33.
14. Lind AR, McNicol GW. Muscular factors which determine the cardiovascular responses to sustained and rhythmic exercise. *Can Med Assoc J* 1967;**96**(12):706–15.
15. Crandall CG, Vongpatanasin W, Victor RG. Mechanism of cocaine-induced hyperthermia in humans. *Ann Intern Med* 2002;**136**:785–91.
16. Bachmann RF, Wang Y, Yuan P, Zhou R, Li X, Alesci S, et al. Common effects of lithium and valproate on mitochondrial functions: protection against methamphetamine-induced mitochondrial damage. *Int J Neuropsychopharmacol* 2009;**12**(6):805–22.
17. Clay HB, Sillivan S, Konradi C. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. *Int J Dev Neurosci* 2011;**29**(3):311–24.
18. Ruttenber AJ, McAnally HB, Wetli CV. Cocaine-associated rhabdomyolysis and excited delirium: different stages of the same syndrome. *Am J Forensic Pathol* 1999;**20**(2):120–7.
19. Miller ML. *Causes of rhabdomyolysis*. In: UpToDate. Romain PL, ed. UpToDate. Waltham, Mass. UpToDate;2012. Last updated: December 22, 2011. Available at: http://www.uptodate.com. [accessed 07.06.12].
20. Stratton SJ, Rogers C, Brickett K, Gruzinski G. Factors associated with sudden death of individuals requiring restraints for excited delirium. *Am J Emerg Med* 2001;**19**:187–91.
21. Edgcombe H, Carter K, Yarrow S. Anaesthesia in the prone position. *Br J Anaesth* 2008;**100**:165–83.
22. Neira VM, Gardin L, Ryan G, Jarvis J, Roy D, Splinter W. A transesophageal echocardiography examination clarifies the cause of cardiovascular collapse during scoliosis surgery in a child. *Can J Anaesth* 2011;**58**:451–5.
23. Lee BK, Vittinghoff E, Whiteman D, Park M, Lau LL, Tseng ZH. Relation of Taser (electrical stun gun) deployment to increase in in-custody sudden deaths. *Am J Cardiol* 2009;**103**(6):877–80.
24. Giammarco RA. The athlete, cocaine, and lactic acidosis: a hypothesis. *Am J Med Sci* 1987;**294**(6):412–4.
25. Sardão VA, Pereira SL, Oliveira PJ. Drug-induced mitochondrial dysfunction in cardiac and skeletal muscle injury. *Expert Opin Drug Saf* 2008;**7**(2):129–46.
26. Capacchione JF, Muldoon SM. The relationship between exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia. *Anesth Analg* 2009;**109**:1065–9.
27. Butt MV, Sailhamer EV, Li Y, Liu B, Shuja F, Velmahos GC, et al. Pharmacologic resuscitation: cell protective mechanisms of histone deacetylase inhibition in lethal hemorrhagic shock. *J Surg Res* 2009;**156**(2):290–6.

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